

## SYSTEMATIC REVIEW

**Traditional Chinese Medicine for the treatment of influenza: a systematic review and Meta-analysis of randomized controlled trials**

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were identified and reviewed. Of these trials, 2 compared a (modified) prescription of TCM with oseltamivir and 5 compared a patent traditional Chinese drug with oseltamivir. Based on the Meta-analysis, compared to oseltamivir, the (modified) prescription had similar effect in defervescence [ $WMD = 5.66$ , 95%  $CI (-32.02, 43.35)$ ,  $P = 0.77$ ] and viral shedding [ $WMD = -6.21$ , 95%  $CI (-84.19, 71.76)$ ,  $P = 0.88$ ], and the patent traditional Chinese drug also had similar effect in viral shedding [ $WMD = -0.24$ , 95%  $CI (-4.79, 4.31)$ ,  $P = 0.92$ ] but more effective in defervescence [ $WMD = -4.65$ , 95%  $CI (-8.91, -0.38)$ ,  $P = 0.03$ ].

**CONCLUSION:** TCM has potential positive effects in the treatment of influenza.

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**Key words:** Influenza, human; Medicine, Chinese Traditional; Oseltamivir; Systematic review; Randomized controlled trials**Abstract****OBJECTIVE:** To justify the clinical use of Traditional Chinese Medicine (TCM) in the treatment of influenza.**METHODS:** MEDLINE, EMBASE, Chinese Biomedical Literature Database, China National Knowledge Infrastructure Database, China Science and Technology Journal Database, Wanfang Database and the Cochrane Database of Systematic Reviews were searched from the date of inception until January 1, 2013, for the literature on treatment of influenza with TCM.**RESULTS:** A total of 7 randomized controlled trials**INTRODUCTION**

Up to now, the threat of pandemic influenza remains an internationally major public health concern.<sup>1</sup> As an important pharmaceutical intervention against the influenza virus, oseltamivir has been widely used against influenza virus infection in the world.<sup>2</sup> It has been demonstrated that oseltamivir can prevent the release of progeny viral particles from infected host cells and shorten the duration of influenza and decrease the development of serious complications.<sup>3,4</sup> However, a major shortcoming of oseltamivir is the emergence of viral resistance.<sup>5</sup> Therefore, it is of crucial importance to find an effective and safety alternative to treat influenza in-

fection, especially in rural areas of China where the supply of oseltamivir is often insufficient.

In China, Traditional Chinese Medicine (TCM) with a history of thousands of years is proved to be effective for the treatment of infectious diseases.<sup>6</sup> Some studies have demonstrated that TCM can be used as an alternative treatment of influenza virus infection.<sup>7-9</sup> In this study, the clinical effect of TCM in the treatment of influenza A virus infection is evaluated through comparison with oseltamivir.

## METHODS

### Search strategy

MEDLINE, EMBASE, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure Database (CNKI), China Science and Technology Journal Database (VIP), Wanfang Database and the Cochrane Database of Systematic Reviews were searched from the date of inception until January 1, 2013. Of these databases, CBM, CNKI, Chinese Scientific Journal Database and Wanfang Database provided literatures in Chinese. In this study, "Traditional Chinese Medicine", "oseltamivir" and "influenza" were designed for the search. Reference lists from retrieved documents were also searched.

### Criteria of inclusion

Subjects older than 3 years and hospitalized with a clinical or laboratory diagnosis of influenza infection were included in this study. Other inclusion criteria were: (a) study design: randomized controlled trial; (b) intervention: treatment group with a relatively fixed prescription of TCM or a patent traditional Chinese drug and control group with oseltamivir; (c) human studies.

### Quality control

Data were independently extracted from each study using pre-defined forms by two investigators, and disagreement was resolved by discussion among investiga-

tors and reference to the original article. When several publications pertaining to a single study were identified, the most complete publication was used. The concrete assessments were seen in the article<sup>10</sup> (Jadad score).

### Efficacy measures

Efficacy was measured with duration of fever and viral shedding. The safety of treatment was also assessed.

### Data analysis

Data analysis was carried out using Review Manager Software 4.2<sup>11</sup> (Cochrane Collaboration, Oxford, United Kingdom). The effect measures estimated were weighted mean difference (WMD), reported with 95% confidence intervals (CI). Fixed-effect or random-effect method in the analysis depended on the absence or presence of significant heterogeneity which was evaluated by the *Chi*-square and *I*-square (*I*<sup>2</sup>) tests. In the absence of statistically significant heterogeneity, the fixed-effect method was used to combine the results. When heterogeneity was confirmed, the random-effect method was used. The overall effect was tested using *Z* scores, with significance set at  $P < 0.05$ .

## RESULTS

### Selection and characteristics of study

Searches resulted in 2132 unique articles. Finally, 7 randomized controlled trials (RCTs) were left for analysis.<sup>12-18</sup> Figure 1 shows the flow chart of study selection process. 2 trials compared the efficacies between (modified) Yinqiao powder and oseltamivir and the total number of patients involved was 93.5 trials compared the efficacies between Lianhuaqingwen capsule and oseltamivir and the total number of patients involved was 607. Table 1 summarizes the main characteristics of the included studies.

### Clinical outcomes

Comparison of the effect of Yinqiao powder with oseltamivir: 2 trials in which the effect of Yinqiao powder

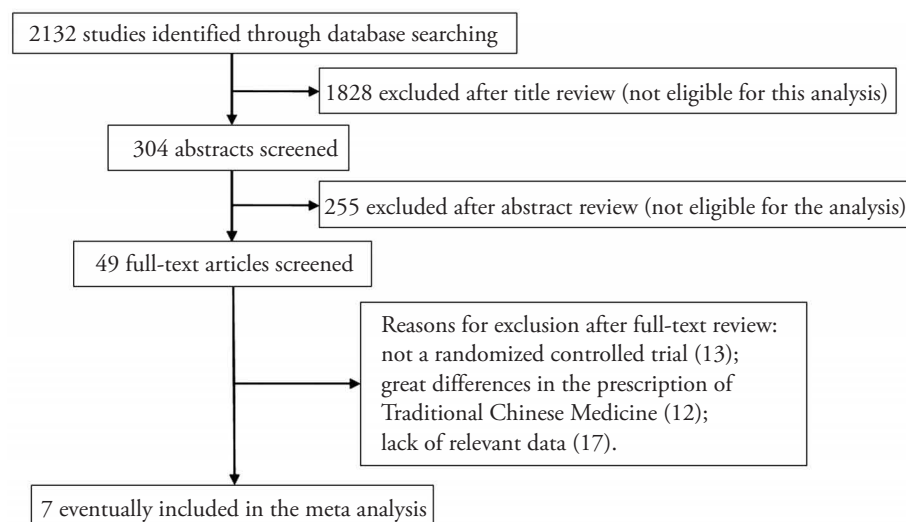


Figure 1 Flowchart of study selection process

Table 1 Main characteristic of the included trials

Study	Sample and intervention		Study design	Jadad score
	Treatment group	Control group		
Zhang WS <i>et al</i> 2011 <sup>12</sup>	30 cases were treated with (modified) Yinqiao powder	30 cases were treated with oseltamivir	RCT, blind unclear	2
Zheng HP <i>et al</i> 2010 <sup>13</sup>	14 cases were treated with (modified) Yinqiao powder	19 cases were treated with oseltamivir	RCT, blind unclear	2
Duan ZP <i>et al</i> 2011 <sup>14</sup>	122 cases were treated with Lianhuaqingwen capsule	122 cases were treated with oseltamivir	RCT, double-blind	5
Ma YP <i>et al</i> 2010 <sup>15</sup>	60 cases were treated with Lianhuaqingwen capsule	74 cases were treated with oseltamivir	RCT, blind unclear	2
Liu GX <i>et al</i> 2010 <sup>16</sup>	64 cases were treated with Lianhuaqingwen capsule	60 cases were treated with oseltamivir	RCT, blind unclear	2
Li BF <i>et al</i> 2009 <sup>17</sup>	25 cases were treated with Lianhuaqingwen capsule	25 cases were treated with oseltamivir	RCT, double-blind	3
Geng LM <i>et al</i> 2011 <sup>18</sup>	38 cases were treated with Lianhuaqingwen capsule	30 cases were treated with oseltamivir	RCT, blind unclear	2

Note: RCT: randomized controlled trials.

on influenza was compared with oseltamivir were included in the analysis.<sup>12,13</sup> There was no statistical difference between the two groups in duration of fever [ $WMD=5.66$ , 95%  $CI$  ( - 32.02, 43.35),  $P=0.77$ ] or in duration from onset to negativity of viral RNA [ $WMD= - 6.21$ , 95%  $CI$  ( - 84.19, 71.76),  $P=0.88$ ]. Figure 2 shows the forest plot of effect comparison of Yinqiao powder versus oseltamivir.

Comparison of the effect of Lianhuaqingwen capsule with oseltamivir: 5 trials in which the effect of Lianhuaqingwen capsule on influenza were compared with oseltamivir were included in the analysis.<sup>14-18</sup> Shorter fever duration was shown in the Lianhuaqingwen capsule group as compared with that in the oseltamivir group, with a statistically significant difference between the two groups [ $WMD= - 4.65$ , 95%  $CI$  ( - 8.91, - 0.38),  $P=0.03$ ]. Regarding the viral shedding, there was no statistical difference between the two groups in duration from onset to negativity of viral RNA [ $WMD= - 0.24$ , 95%  $CI$  ( - 4.79, 4.31),  $P=0.92$ ]. Figure 3 shows the forest plot of effect comparison of Lianhuaqingwen

capsule versus oseltamivir.

Safety: in the included patients treated with Yinqiao powder, Lianhuaqingwen capsule or oseltamivir, no significant drug-related serious adverse events such as neuropsychiatric events, including delirium and abnormal behavior, were reported.

## DISCUSSION

As an alternative therapy, TCM focuses on the treatment of human disease *via* the integrity of the close relationship between body and syndrome analysis and becomes increasingly more popular worldwide because of its "miraculous" curative effect.<sup>19</sup> Yinqiao powder is a traditional Chinese prescription mainly composed of Jinyinhua (*Flos Lonicerae*), Lianqiao (*Fructus Forsythiae Suspensae*), Bohe (*Herba Menthae Haplocalycis*), *et al.* Lianhuaqingwen capsule is a Chinese patent medicine composed of honey-fried Mahuang (*Herba Ephedra Sinica*), Kuxingren (*Semen Armeniacae Amarum*), Lianqiao

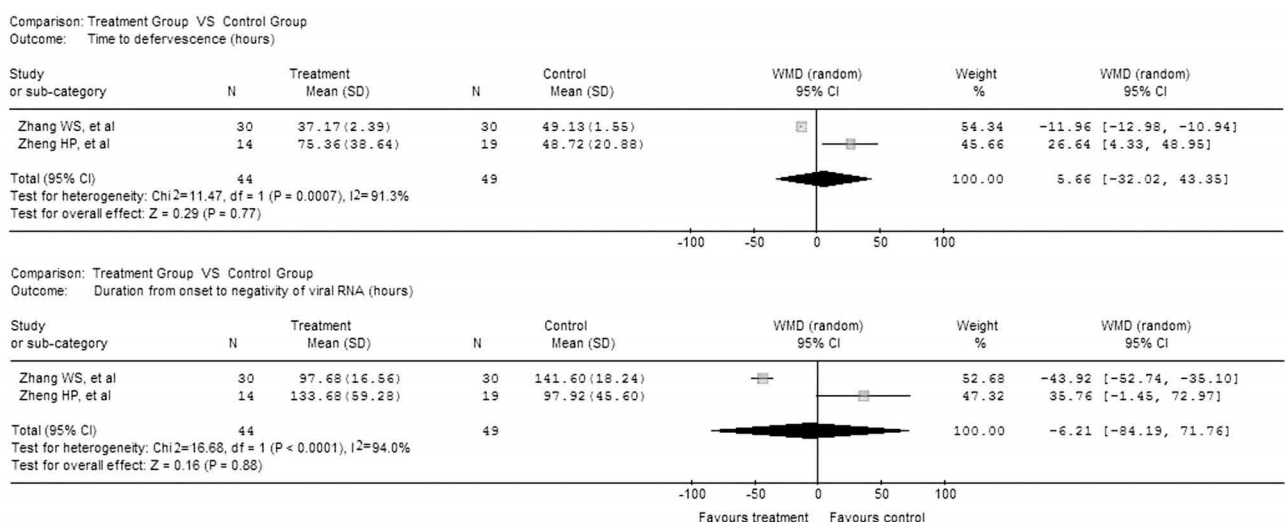


Figure 2 Forest plot of effect comparison of Yinqiao powder vs oseltamivir on the time to defervescence

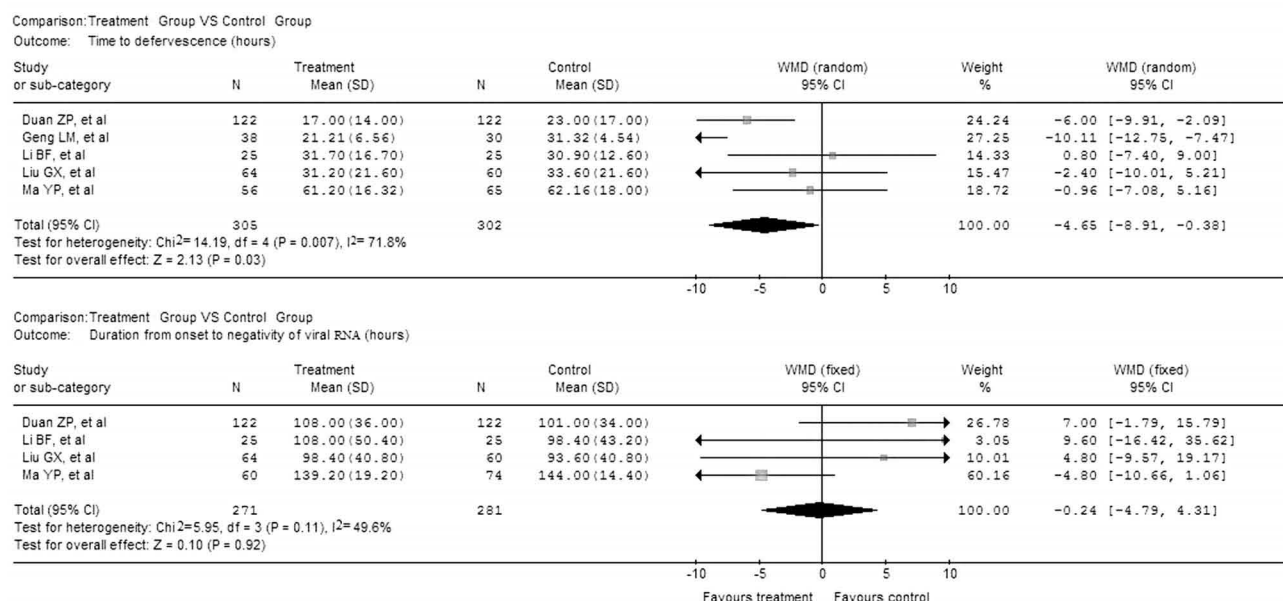


Figure 3 Forest plot of effect comparison of Lianhuaqingwen capsule vs oseltamivir

(*Fructus Forsythiae Suspensae*), Bohe (*Herba Menthae Haplocalycis*), et al. Because the mechanism of TCM in the treatment of influenza is complex, it is difficult to determine which ingredient plays the main roles in anti-influenza virus infection. However, it is well known that some Chinese herbs can suppress the viral replication and may have beneficial immunomodulatory effects for rapid recovery of viral infections.<sup>20-22</sup>

Based on the outcomes from our Meta-analysis, the (modified) Yinqiao powder had similar effect with oseltamivir in defervescence and viral shedding; the patients treated with Lianhuaqingwen capsule had shorter duration of fever than the patients treated with oseltamivir and the efficacy of the two treatments on viral shedding was similar. Some severe adverse events were not observed in both the two groups in our included studies, though these events had been reported in post-marketing surveillance for oseltamivir.<sup>23</sup> Concerning the adverse effect, we found that the report from most of the included studies was inadequate, which was a major limitation of our study.

In conclusion, compared to oseltamivir, TCM has potential positive effect in the treatment of influenza.

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